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THE EFFECT OF POTASSIUM IODID ON EXPERIMENTAL SPOROTRICHOSIS

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The relatively large number of human cases of sporotrichosis now observed has furnished abundant opportunity for testing the effect of potassium iodid on the course of this infection. Almost without exception such cases respond promptly to its administration in doses of 30-40 grains per day and usually a complete cure follows in the course of a few weeks. Its administration is continued some little time after complete healing is apparent since otherwise a recurrence is apt to follow. It has also been shown by Carongeau¹ that horses and mules, which are naturally susceptible to this disease, likewise respond promptly to this drug. The results, on the whole, show that the iodids in sporotrichosis furnish one of the best examples of a specific therapeutic agent known.

One is impressed with the difference between the prompt reaction to potassium iodid of sporotrichotic patients and the effect of potassium iodid in other similar infections like blastomycosis, actinomycosis and tuberculosis, in which cases the reaction is irregular and uncertain and may be beneficial, indifferent, or possibly harmful.

I wish to record in this paper certain experiments to test the action of the iodids on the course of experimental infection in animals produced with typical strains of *Sporotrichum schenckii*.

First, I will call attention to the relative inertness of potassium iodid and of iodine so far as their direct germicidal power on sporotricha is concerned as illustrated in table 1.

It will be observed that potassium iodid has very little direct effect on the life of *Sporotrichum schenckii*. In a 10% solution the organisms live for at least 48 hours and in the 1% solution and in those of lesser concentration the organisms were alive at the end of 74 days at which time this experiment was discontinued. In distilled water they were also alive at the end of this time. A strain of

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¹ Quoted from de Beurmann et Gougerot, *Les Sporotrichoses*, Paris, 1912.

Sporotrichum schenckii was used which had been isolated from a human lesion a few months previously and at the time was pathogenic for rats. The culture was a vigorous growing one about 4 weeks old. At the varying intervals indicated in the table, 0.1 c c of the sporotrichum suspension was removed from each of the tubes and inoculated on glucose agar and the readings made after 3 weeks.

TABLE 1
GERMICIDAL ACTION OF AQUEOUS SOLUTION OF POTASSIUM IODID ON SPOROTRICHUM SCHENCKII (CULTURE ONE MONTH OLD)

Time	0.1% KI	0.5% KI	1% KI	2% KI	5% KI	10% KI	Water
1 minute	+++	+++	+++	+++	+++	+++	+++
15 minutes	+++	+++	+++	+++	+++	+++	+++
1 hour	+++	+++	+++	+++	+++	++	+++
24 hours	++	++	++	+++	++	++	++
48 hours	++	++	++	++	++	+	+++
96 hours	++	++	++	++	++	0	++
5 days	++	++	++	+	+	0	++
8 days	++	++	++	++	++	0	++
11 days	+++	+++	+++	+	++	0	+++
17 days	++	+++	+++	0	0	0	+++
23 days	++	++	++	++	0	0	++
32 days	++	++	++	++	0	0	++
47 days	++	++	++	0	0	0	++
56 days	++	++	++	0	0	0	++
74 days	++	++	++	0	0	0	++

These results are sufficient to indicate that iodine either in the form of potassium iodide or in a free form in the culture medium has very little germicidal effect on this fungus even in relatively high concentrations. The concentrations which the iodine attains in the body when administered therapeutically probably does not approach the concentrations in which the growth is inhibited in experiment, and could therefore, through its direct action, have no appreciable effect.

TABLE 2
EFFECT OF POTASSIUM IODIDE AND TINCTURE OF IODINE IN 1% GLUCOSE AGAR ON THE GROWTH OF SPOROTRICHUM SCHENCKII AND A BLASTOMYCES

Percentage of Potassium Iodide and Tincture of Iodine	Sporotrichum schenckii		Blastomyces		Schenk-Hektoen Strain (original)
	Tincture of Iodine	Potassium Iodide	Tincture of Iodine	Potassium Iodide	
10	0	++	0	+	0
5	0	+++	0	++	0
4	0	+++	0	+++	0
3	0	+++	0	+++	0
2	0	+++	0	+++	0
1	0	+++	+	+++	+
0.5	++	+++	++	+++	+
0.2	++	+++	+++	+++	++
0.1	+++	+++	+++	+++	+++

Another experiment was made by adding potassium iodid and the tincture of iodine in varying concentration to a series of tubes containing 1% glucose agar. Table 2 gives the results. It will be seen that even in as high a concentration as 10% of potassium iodid the organisms grew very well and in all concentrations below that amount there developed a profuse growth. In the medium containing tincture of iodine one strain of *sporothrix* grew in 1% concentration and below, another grew at 5% and below. In 2% strengths and above there was no growth.

To throw further light on the possible mechanism of the action of potassium iodid in this infection a series of white rats approximately 100 gm. in weight was given the drug subcutaneously before, simultaneously with and after inoculation with a virulent strain of *Sporothrichum schenckii*. The strain had recently been isolated from a typical human case of sporotrichosis and was a good pigment producer and virulent. The *sporotrichum* was grown for 3 weeks on glucose agar, the growth was scraped from the surface and macerated in salt solution thereby obtaining a turbid suspension of spores and mycelium. In the following experiments 1 cc of this suspension was used uniformly in all the animals inoculated in the different series so that the experiments would be comparable.

1.—On March 12, two white rats were inoculated intraperitoneally as controls. April 10, small nodes on abdomen at points of inoculation. Nodules in abdomen large; animals not lively, and visibly affected. April 30, both killed; a large firm nodule in abdominal wall at the point of inoculation; peritoneum studded especially on the omentum, mesentery and bowel with numerous gray, firm nodules. Liver and lungs not involved. In smears of the crushed nodules were seen the oblong tissue forms and in cultures of this material numerous colonies of *sporotricha* appeared after a few days. Both rats presented almost identical findings. Other experiments previously made had likewise shown this particular strain of *sporotrichum* to be uniformly virulent for rats.

2.—Two white rats were given subcutaneously 0.05 gm. of a solution of potassium iodid each day for 8 successive days. On the last day (March 12) an intraperitoneal inoculation of 1 cc of the *sporotrichum* was given also. The potassium iodid was now discontinued. On April 10 the animals were in fair condition but somewhat thin. On April 28 both animals had large swollen, nodular, fixed testicles and one had nodes on the abdominal wall. One died May 18, the other on June 5. Both revealed similar findings, namely, extensive nodular lesions of peritoneum and viscera and extensive involvement of the bones of front and hind extremities. One weighed 60 gm., the other 72 gm. Cultures of heart blood were sterile. Cultures of the nodes and bones were profusely positive. The infection in these animals following the use of potassium iodid made as rapid, possibly a little more rapid, progress than in those of the control series.

3.—On March 12, two rats were each injected intraperitoneally with the sporotrichum and at the same time and on each of 6 successive days 0.05 gm. of potassium iodid was given, also intraperitoneally. Up to April 28 no symptoms, but at that time they showed some evidence of weakness and emaciation. One died on July 9, and showed typical sporotrichotic nodules on various parts of omentum, peritoneum and intestine. The nodes were softened; and smears and cultures from the interior showed many sporotricha. On July 12, the other rat being weak and sickly was chloroformed and revealed findings almost identical with the first rat. Evidently, then, the administration, simultaneously and on 6 successive days, was not sufficient to protect the rats, the infection going on very much the same as in the controls.

4.—On March 12, two rats were given intraperitoneally, injections of sporotricha and one month later (April 11) were given 0.05 gm. of potassium iodid continuously each day (excepting Sundays) subcutaneously. Shortly after the injection the rats became sickly and weak, and on April 10 their testicles were large, nodular and red. Both were evidently quite ill. Following the iodid, however, they soon improved gradually, and on April 28 seemed quite well excepting that one was somewhat emaciated, having lost about 15 gm. The testicles were much smaller but were nodular and firm. On May 7, one of the rats was found dead; cause of death undetermined. A few small, hard, white nodes in the mesentery and about the testicles were found. The involvement was not extensive; other viscera not involved. A few of these firm nodes from the mesentery were incised and crushed and cultures made yielded a decided growth. The heart blood was sterile. On June 4 the second rat having had potassium iodid continuously was quite well and was killed. Necropsy revealed similar nodules, hard, firm and small, especially about the testicles. A few small nodes were found also about the hind limb bones. The gross appearance of these nodes was that of a healing lesion. On cultures, however, the crushed nodes of the bone and peritoneum yielded a good growth of sporotricha. Evidently the lesions in these animals were healing though the organisms still remained alive within.

5.—Two white rats, on March 12, were injected with 1 cc intraperitoneally and at the same time with 1 cc subcutaneously just above the tail. About three weeks later, on April 4, nodules appeared on the belly at the site of inoculation, and over the tail was a large open ulcer 1.5 cm. across and with raised margins. Cultures from the deeper parts yielded a profuse growth of sporotricha. At this date 0.05 gm. doses of potassium iodid were commenced subcutaneously and continued daily. On April 9, four days later, the lesion over the tail was softer and smaller and on one rat a scab was forming. On April 14, the lesions in both animals were rapidly healing but cultures from them were still profusely positive. At this time 1 cc of culture of sporotricha was injected into each rat under the skin of the neck near the right shoulder; also about 2 drops under the skin of the tail about 3 cm. from its base. The potassium iodid was continued. The old lesion above the tail became smaller gradually but at the site of the new injections the lesions appeared which were red and swollen and edematous; they continued, both in the neck and on the tail of each rat, to progress for about 3 weeks then gradually receded. During this period, then at a time when the animal was receiving potassium iodid, the old lesions were healing, whereas the fresh lesions were progressing. The animals continued to improve and later all the lesions showed healing. On June 21, nine weeks after the last injections, the cutaneous lesions were practically well and from then until

July 10 the potassium iodid was given every other day, at which time the animals were killed, having been under observation for 4 months. They appeared quite normal and were not emaciated. On necropsy, both animals presented hard, small, whitish gray nodes in the peritoneum and mesentery about 0.1 mm. or less in diameter. On section these small lesions revealed a slight softening and on smear and culture sporotricha were obtained in considerable numbers. Also in one of the rats at the site of the neck lesion was a small node just visible which earlier had been as large as a cherry. This lesion had contracted and healed, but cultures from its center still revealed live sporotricha in considerable numbers. The lesions in the skin on and above the tail had practically disappeared.

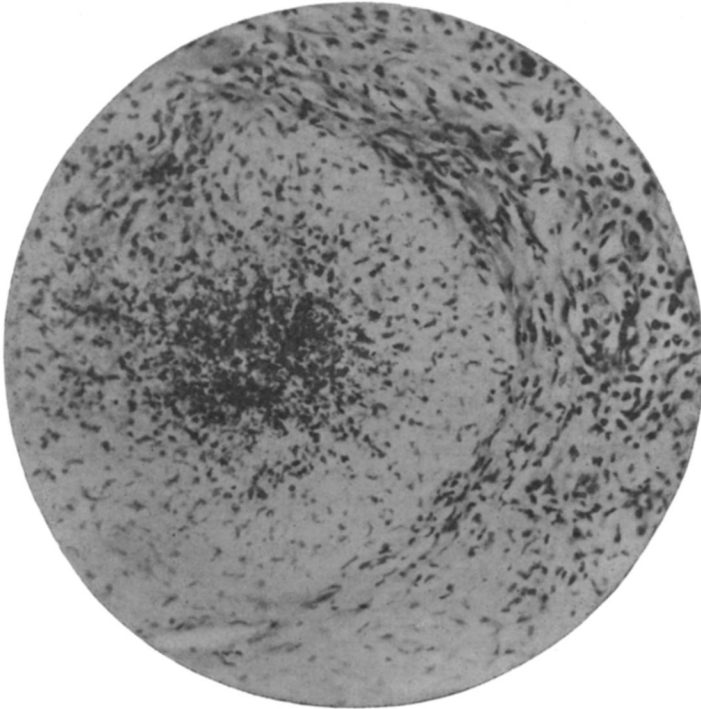


Fig. 1.—Encapsulated sporotrichotic nodule from the omentum of a rat following administration of potassium iodid.

Sections were made of these hard lesions, a photograph of which is shown in Fig. 1. The dense fibrous capsule is seen and in the center is still some necrotic tissue in which occur the organisms. In Fig. 2 are to be seen small recent sporothrix lesions in the liver of a rat for comparison.

It would appear that the lesions under the influence of the potassium iodid become smaller and harder and a marked increase in connective tissue occurs which tends to wall off the organisms. However, the potassium iodid does not appear to have any appreciable

direct effect in killing sporotricha for they were still found in centers of the hardened nodules several months later. This is in accord with the experimental data presented earlier in the paper which showed little or no direct action on the organisms.

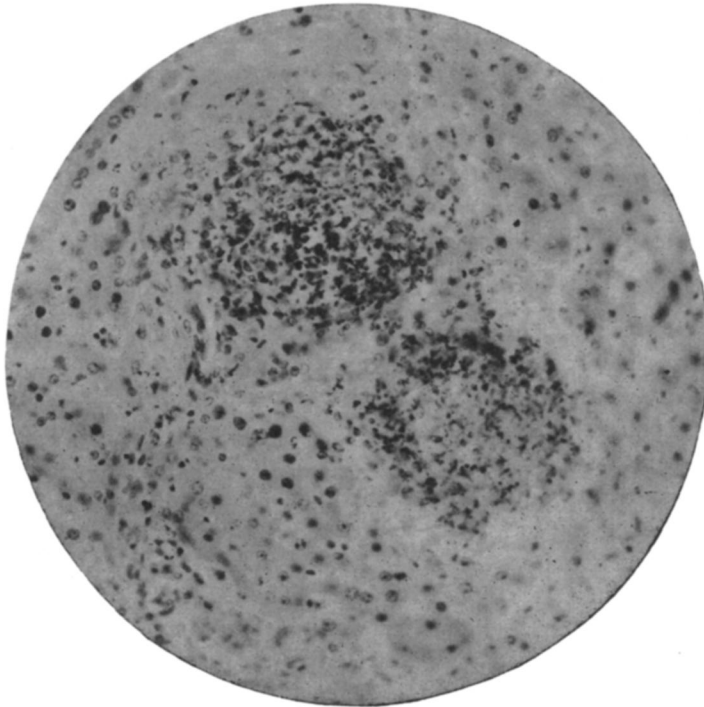


Fig. 2.—Sporotrichotic nodule in the liver of a white rat suffering from a progressive sporotrichosis without treatment.

DISCUSSION

The experiments indicate that potassium iodid given to animals for 8 days previous to inoculation with sporotricha will have no effect in inhibiting or preventing the infection. Also, when given simultaneously and for a week following the inoculation, the infection appears to continue without interruption. When the potassium iodid is continued indefinitely the lesions heal becoming hard and contracted, but the sporotricha remain alive in their centers for a long time and apparently are unable to disseminate.

Lesions following inoculation under the skin usually progress, but if potassium iodid is administered they gradually recede; such lesions

can be inspected from day to day and the healing process observed. By reinoculating such an animal, even when receiving potassium iodid, the new infection will progress for a period of 2 or 3 weeks and then recede so that it is possible to have in one and the same animal, one lesion which is healing under the influence of potassium iodid and another which is progressing. Evidently the potassium iodid does not act in a direct way on the sporotricha, but indirectly through the agency of tissue proliferation and processes incidental thereto.

From the experiments it seems clear that potassium iodid acts in such a way as to stimulate the healing process without inhibiting the development of the infecting organism. In other words, its action is curative and not preventive. De Beurmann and Gougerot have pointed out practically the same fact in connection with their studies of *Sporotrichum beurmanni*, their experiments also indicating that potassium iodid acts in a curative rather than in a preventive way. They contend, however, that *Sporotrichum schenckii* is different from *Sporotrichum beurmanni*. Without here entering into a discussion of this point, it may be stated that many facts indicate their identity including the reaction of the two infections to potassium iodid not only in animals but in human cases.

In my experiments potassium iodid was used, but other compounds of iodine or free iodine would probably behave in the same way. Sollmann² has shown that no matter in what form iodine is given it circulates in the blood and is excreted in the form of the iodid. He also states, what is important in connection with the action of potassium iodid on sporotrichum infections, that it is impossible under any conditions existing in the body (excepting solely the gastric juice) for free iodine to be liberated from iodid. This is in entire accord with the results of my experiments, all of which tend to show that iodine does not act directly on the organisms.

As to other possible mechanisms by which iodine acts in the body that developed by Lortat-Jacob³ and advocated by many French workers is interesting in this connection. Lortat-Jacob contends that the leukocytes are the active agents in the absorption of iodids or iodine after peritoneal or subcutaneous injection. The iodine can actually be seen coloring the cells and may be detected by the starch method. After peritoneal injection an endothelial reaction with

² Cleveland Med. Jour., 1916, 15, p. 792.

³ Thèse, 1903, Paris.

accumulation of endothelial leukocytes occurs. He maintains that this reaction, especially of the mononuclear and lymphoid tissue, by their defensive properties permits an explanation of the good effects of iodine in chronic infections. He says that under the influence of iodine there is congestion and hyperactivity of the lymphoid tissue and repeated small doses may lead to sclerosis of tissues. The French, it is interesting to note, have used and continue to use iodine in tuberculosis especially of the glandular type with what they consider encouraging results.

Wells and Hodenbergh⁴ have shown that tuberculous as well as other necrotic tissues take up more iodine than normal tissue because the dead cells are more permeable to iodids. But they obtain no evidence that iodine tends to become specifically fixed in inflammatory exudates. It is distributed by a process of simple diffusion. Heinz⁵ noted an active exudative inflammation following the injection of iodine in the body cavities and Hirsch⁶ observed an increased fibrous tissue reaction about masses of fat-free tubercle bacilli treated with an iodine solution. Jobling and Peterson⁷ have called attention to the possible rôle of iodine in tuberculosis and other infections in saturating the unsaturated fatty acid soaps which act as antiferments, thereby permitting the tryptic enzymes to digest the cells and tissues and to remove caseous matter. This increased ferment activity may play a rôle in the cure of sporotrichosis by iodids. Natural or experimental sporotrichosis might furnish excellent material for testing this hypothesis further.

SUMMARY

Experimental sporotrichosis in rats responds promptly to potassium iodid.

The lesions in the peritoneal cavity become firm, hard and small and are surrounded by a dense fibrous capsule; within the nodules living sporotricha are found for a long time (at least 4 months).

Potassium iodid will not prevent experimental sporotrichosis but will cure it.

It is suggested that sporotrichosis, so readily produced experimentally, furnishes a good opportunity for the study of the behavior and reactions of iodine and iodids in chronic infections.

⁴ Jour. Infect. Dis., 1912, 11, p. 439.

⁵ Virchow's Archiv, 1899, 155, p. 44.

⁶ Jour. Infect. Dis., 1914, 15, p. 487.

⁷ Jour. Exper. Med., 1914, 19, p. 383.